Itch (pruritus) Outline

• History of Itch
• Defining Itch
• Biophysics of Itch
• Pathology of Itch
Earliest research

First clinical definition of itch: German Physician Samuel Hafenreffer (1587–1660).

Original idea: Low level nociceptor activation → sensation of itch

Higher level nociception → pain sensation (von Frey, 1922 intensity theory)
Chronology of itch research

1927 Histamine’s role in injury and possibly itch. Lewis T, Zotterman Y. (1927)

1955 Histamine-induced pruritus and pain. Broadbent JL. (1955)

1960 Pruritus via particular pattern of activation hypothesis (Wall and Cronly-Dillon, 1960) (i.e. the firing of pain receptors through specific pattern of activation; that pattern is recognized in the brain as “itch” and there the sensation of “itch” is felt!)
Chronology of itch research

• 1992 Pruritus via activation of a subpopulation of polymodal C-fibers hypothesis (Tuckett and Wei, 1987; Handwerker, 1992)

• 1997 Specific C-Receptors for Itch in Human Skin (Schmelz et al. 1997)

• 2007 More than just histamine pathway?
Defining itch

Classic Definition:

Unpleasant sensation that elicits the desire or reflex to scratch.

Twycross Clinical classification:

*Pruritoceptive itch* (originating from the skin)

*Neurogenic itch* (originating along afferent pathway)

*Neuropathic itch* (originating from disease along the afferent pathway)
Itch categorization.

1. Source: peripheral or central
2. Source: localized or general
3. Response: Histamine / non-histamine related
Neurogenic itch (originates centrally without neuropathy...)

Pruritus in Cholestasis

- Liver Derived Pruritogen
- Gut Derived Pruritogen
- Bile Acids

Central Itch Modulators

Descending Inhibitory Neural Pathways
Neuropathic itch

e.g. Psychogenic itch: Caused by psychological problem (e.g. parasitophobia)
Itch source may be chronic or acute

Acute: mosquito bite

Chronic: atopic dermatitis
Itch source may be localized or systemic

For example, cancer or organ failure can lead to itch sensation.
Histaminergic or histamine-independent itch

Strong non-histaminergic (and nasty!) itch produced by Cowhage plant (*Mucuna pruriens*)
Itch and Pain Similarities

- Afferent sensory neurons both unmyelinated C-fibers
- Peripheral itch and pain fibers associated with mast cells.
- Both are unpleasant sensory experiences.
- Chronic pruritic patient: painful stimulus can evoke itch sensation
- Chronic pruritic patients & chronic pain patients:
  - Increased NGF (nerve growth factor) release
  - Increased NT4 (neurotrophin 4) release
  - Increased intradermal nerve fiber density
Itch and Pain:

Itch inhibited by pain & itch sensation enhanced by inhibiting pain

μ-opioids are pruritogenic
κ-opioids are antipruritogenic

MARTIN SCHMELZ (2005) Itch and Pain, Figure 1
Cross-modal itch modulation

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Effects on peripheral endings</th>
<th>Spinal effects</th>
<th>Psychophysical result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold</td>
<td>Inhibition</td>
<td>Inhibition</td>
<td>Antipruritic</td>
</tr>
<tr>
<td>Warmth</td>
<td>Fascilitation</td>
<td>?</td>
<td>Pruritic</td>
</tr>
<tr>
<td>Noxious heat</td>
<td>Nociceptor activation</td>
<td>Inhibition</td>
<td>Antipruritic</td>
</tr>
<tr>
<td>μ-opioids</td>
<td>Histamine release</td>
<td>Disinhibition</td>
<td>Pruritic</td>
</tr>
<tr>
<td>κ-opioids</td>
<td>Histamine release</td>
<td>Inhibition</td>
<td>Antipruritic</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>Neurotoxic</td>
<td>Inhibition</td>
<td>Antipruritic</td>
</tr>
</tbody>
</table>

May only be noxious cold that works (Yosipovitch, 2005). All work done on histamine-induced itch in human.
The Itch Receptor

Like pain, itch mediated by slow conducting unmyelinated C-fibers (...and slower than pain fibers).

Physiologically, itch fibers are heat/cold & mechanically insensitive.
Instantaneous discharge frequency of a mechano- and heat-insensitive C-fiber (CMiHi), superficial peroneal nerve, following histamine iontophoresis.

\[
\text{Histamine} \quad \text{HN} \quad \text{C} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{NH}_2
\]
Mast cell & C-fibers interaction

Mast cell activation → histamine release → itch & sensitization.

TNF=tumour necrosis factor; TNF-R=TNF receptor; H1=histamine H1 receptor; PAR=proteinase activated receptor; NK1=neurokinin receptor 1; SP=substance P; VR1=vanilloid receptor 1

Yosipovitch et al. (2003) Itch Figure 2
Histamine as direct agent too simple: anti-histamines are typically ineffective in treating chronic pruritis.
Pain & itch share multiple modulators

Blue: mainly nociception
Red: mainly Pruritic
Yellow: prevalent in both

Akihiko Ikoma et al. 2006 the Neurobiology of itch, figure 1
Non-histaminergic pruritis: Protease-activated Receptor.

Chronic itch patients have upregulated levels of PAR-2.

Cleave receptor extracellular domain $\rightarrow$ activated receptor (PAR2). Various plants, bacteria secrete appropriate proteases.
Mast cells also involved in non-histaminergic pruritis.

Mast cell $\rightarrow$ tryptase $\rightarrow$ attack membrane receptor $\rightarrow$ PAR2 activation.

Demonstrated effect in patients suffering from atopic dermatitis (Steinhoff et al. 2003)
Other “usual” suspects…

<table>
<thead>
<tr>
<th>Neuromediator</th>
<th>Receptor</th>
<th>Source</th>
<th>Role in itch</th>
<th>Role in pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGF</td>
<td>TrkA</td>
<td>Keratinocytes, mast cells, fibroblasts and eosinophils</td>
<td>Peripheral sensitization in atopic dermatitis\textsuperscript{13,14,41}; Anti-NGF is antipruritic\textsuperscript{40}</td>
<td>Peripheral and central sensitization\textsuperscript{10,201}; Upregulation of TRPV1 (REF. 30); Upregulation of substance P and CGRP\textsuperscript{42}; Anti-NGF analgesic\textsuperscript{88,36}</td>
</tr>
<tr>
<td>Interleukin 31</td>
<td>gp130-like receptor</td>
<td>T-cells and macrophages</td>
<td>Pruritic in the skin\textsuperscript{47,80}, Increased expression in atopic dermatitis\textsuperscript{63}</td>
<td>Not clear</td>
</tr>
<tr>
<td>Opioids</td>
<td>(\mu), (\kappa), (\delta)-opioid receptors (partly receptor-independent T-cell activation)</td>
<td>Neurons and keratinocytes</td>
<td>Antipruritic in the skin (\textsuperscript{?}). At the spinal level, (\mu)-opioids are pruritic\textsuperscript{15}, (\kappa)-opioids are antipruritic\textsuperscript{73,75}</td>
<td>Analgesic in the skin, and at the spinal and supraspinal level\textsuperscript{13,123}</td>
</tr>
<tr>
<td>Endocannabinoids</td>
<td>Cannabinoid receptors</td>
<td>Neurons and keratinocytes</td>
<td>Antipruritic in the skin\textsuperscript{145}</td>
<td>Analgesic in the skin\textsuperscript{142,144,130}, and at the spinal and supraspinal level\textsuperscript{202}</td>
</tr>
<tr>
<td>Endothelins</td>
<td>Endothelin receptors (ET-A and ET-B)</td>
<td>Endothelium and mast cells</td>
<td>Direct pruritic (burning itch)\textsuperscript{203}</td>
<td>Direct algogenic through ET-A Analgesic through ET-B\textsuperscript{204}</td>
</tr>
<tr>
<td>Kallikreins, proteases</td>
<td>Partly by protease-activated receptors (PARs) and tryptic enzymes</td>
<td>Leukocytes, keratinocytes, mast cells, endothelial cells and platelets</td>
<td>Pruritic through PAR\textsubscript{2} (REFS 93, 110, 205)</td>
<td>Neurogenic inflammation through PAR\textsubscript{2} (REF. 90); Thermal and mechanical hyperalgesia through PAR\textsubscript{2}; Analgesic effects of PAR\textsubscript{2}; Thrombin enhances mechanical analgesia and stimulates heat hyperalgesia\textsuperscript{85-87,80}</td>
</tr>
<tr>
<td>Substance P</td>
<td>Neurokinin 1 receptor</td>
<td>Sensory nerve fibres</td>
<td>Priming of mast cells\textsuperscript{46} Pruritic in rodents only\textsuperscript{45,206}</td>
<td>Increase of mast cell TNF\textsubscript{\alpha}; Central sensitization\textsuperscript{13}</td>
</tr>
<tr>
<td>CGRP</td>
<td>CGRP receptors</td>
<td>Sensory nerve fibres</td>
<td>Not clear</td>
<td>Sensitization of primary afferents to heat\textsuperscript{12,13,47}</td>
</tr>
</tbody>
</table>

CGRP, calcitonin-gene-related peptide; NGF, nerve growth factor; TNF\(\alpha\), tumour necrosis factor-\(\alpha\); TrkA, tyrosine receptor kinase A; TRPV1, transient receptor potential vanilloid receptor 1.

Akihiko Ikoma et al. 2006 the Neurobiology of itch, table 2
Pruritic Neuronal Histaminergic Pathway Overall

Example of a “skin” originated itch.

Pruritogen can be anything that causes itch, it can be a range of endogenous signals like amine, proteases, NGFs, etc...

Likely additional pathways.

Twycross et al. (2003) Itch: Scratching more than the surface Figure 1
Histamine-sensitive neurons have also been studied by recording dorsal horn neurons in the cat, and represent a small fraction (about 5%) of spinothalamic projection neurons in the cat.
Some spino-thalamic tract neurons that are mechanically insensitive and respond to histamine with a typical prolonged activation are probably pruritic afferents.

Andrew, D. & Craig, A. D. Spinothalamic lamina 1 neurons selectively sensitive to histamine: a central neural pathway for itch. 2001
In contrast to spinothalamic projection neurons involved in pain processing, the pruriceptive projection neurons do not exhibit spontaneous activity!

Akihiko Ikoma et al. 2006 the Neurobiology of itch, modified from figure 2
Thalamic & cortical nuclei associated with itch.

ACC anterior cingulate cortex,
PFC Prefrontal cortex, Supplementalmotor area,
PAG periaqueductal gray
S1, S2 Primary & secondary somatosensory cortex
SMA, PMA supplemental & premotor areas

Akihiko Ikoma et al. 2006 the Neurobiology of itch, figure 3
Hedonistic Effect – positive effects of scratching.

1. Itch suppression at the spinalthalamic pathway.

2. Itch suppression of unpleasantness in the anterior cingulate cortex.

3. Activation of reward centers in the Putamen.
Topographical differences

The forearm (used most in itch research) isn’t as sensitive to itch as ankle and back.

The forearm also has a lower “pleasurability index”.

G.A. bin Saif et al. (2012) The pleasurability of scratching an itch: a psychophysical and topographical assessment Figure 1
“Contagious” itch

Itch and scratching can be induced through visual stimuli.

...in monkeys too!
Pathological itch
Senile Itch

Itch without any obvious cause occurs in half of the population over the age of 70.

Suspected factors:

1. Lower water content -> dryer skin -> release of local pruritogenic agents

2. Increased sensitivity to histamine, increased mast cell degranulation.
Atopic dermatitis

Predisposition toward developing allergic hypersensitivity.

Causes are still unknown though genetic and environmental factor has often thought to contribute.
Cholestasis

Cholestasis is a condition where bile cannot flow from the liver to the duodenum → often associated with itch.

Plasma extract from patient with cholestasis can induce itch in animals...increases plasma enkephalin.

Note that the liver normally produces endogenous opioid peptides like enkephalins.
Chronic Renal Failure

Also associated with patho itch.

Perhaps related to chronic dry skin & accumulation of interleukins or ?

Sometimes, but not always associated with skin region where dialysis shut inserted.